Comparison of routine prenatal iron prophylaxis and screening and treatment for anaemia

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Comparison of routine prenatal iron prophylaxis and screening and treatment for anaemia: pregnancy results and preliminary birth results from a pragmatic randomised controlled trial (PROFEG) in Maputo, Mozambique

Saara Parkkali,[1] Fatima Abacassamo,[2] Bright Ibeabughichi Nwaru,[3] Graca Salomé,[4] Orvalho Augusto,[2] Elena Regushevskaya,[1] Martinho Dgedge,[5] Cesar Sousa,[2] Julie Cliff,[2] Baltazar Chilundo,[2] Elina Hemminki[1]

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For numbered affiliations see end of article.

Correspondence to
Dr Bright Ibeabughichi Nwaru;
bright.nwaru@uta.fi

ABSTRACT

Objective: To present the pregnancy results and interim birth results of a pragmatic randomised controlled trial comparing routine iron prophylaxis with screening and treatment for anaemia during pregnancy in a setting of endemic malaria and HIV.

Design: A pragmatic randomised controlled trial.

Setting: Two health centres (1° de Maio and Machava) in Maputo, Mozambique, a setting of endemic malaria and high prevalence of HIV.

Participants: Pregnant women (≥18-year-olds; non-high-risk pregnancy, n=4326) attending prenatal care consultation at the two health centres were recruited to the trial.

Interventions: The women were randomly allocated to either Routine iron (n=2184; 60 mg ferrous sulfate plus 400 μg of folic acid daily throughout pregnancy) or Selective iron (n=2142; screening and treatment for anaemia and daily intake of 1 mg of folic acid).

Outcome measures: The primary outcomes were preterm delivery (delivery <37 weeks of gestation) and low birth weight (<2500 g). The secondary outcomes were symptoms suggestive of malaria and self-reported malaria during pregnancy; birth length; caesarean section; maternal and child health status after delivery.

Results: The number of follow-up visits was similar in the two groups. Between the first and fifth visits, the two groups were similar regarding the occurrence of fever, headache, cold/chills, nausea/vomiting and body aches. There was a suggestion of increased incidence of self-reported malaria during pregnancy (OR 1.37, 95% CI 0.98 to1.92) in the Routine iron group. Birth data were available for 1109 (51%) in the Routine iron group and for 1149 (54%) in the Selective iron group. The birth outcomes were relatively similar in the two groups. However, there was a suggestion (statistically non-significant) of poorer outcomes in the Routine iron group with regard to long hospital stay after birth (relative risk (RR) 1.43, 95% CI 0.97 to 1.26; risk difference (RD) 0.02, 95% CI −0.00 to 0.03) and unavailability of delivery data (RR 1.06, 95% CI 1.00 to 1.13; RD 0.03, 95% CI −0.01 to 0.07).

Conclusions: These interim results suggest that routine iron prophylaxis during pregnancy did not confer advantage over screening and treatment for anaemia regarding maternal and child health. Complete data on birth outcomes are being collected for firmer conclusions.

ARTICLE SUMMARY

Article focus

- The benefits of iron prophylaxis during pregnancy on maternal and child health (MCH) in developing country settings with endemic malaria and high prevalence of HIV is unclear.
- Iron has been linked to increased risk of infections.
- Among children less than 3 years, there are indications of harm of universal iron prophylaxis.

Key messages

- Routine iron prophylaxis during pregnancy did not suggest better maternal and child health (MCH) outcomes than screening and treatment for anaemia in a setting of endemic malaria and HIV.

Strengths and limitations of this study

- So far, this represents the largest trial investigating the benefits of prophylactic iron during pregnancy on MCH in malaria-endemic settings.
- The compliance of the study nurses with the trial protocol and that of the women with regard to uptake of the iron and folic acid tablets was good, as was the follow-up during pregnancy.
- The collection of delivery data was challenging, resulting in up to an estimated 40% of missing birth data, which are now been traced using various methods.

Trial registration: The trial is registered at ClinicalTrials.gov, number NCT00488579 (June 2007). The first women were randomised to the trial proper April 2007–March 2008. The pilot was November 2006–March 2008. The 3-month lag was due to technical difficulties in completing trial registration.

INTRODUCTION

Despite the widespread recommendation of routine iron prophylaxis during pregnancy, its benefits and risks for the mother and child, beyond the reduction of the risk of anaemia, remain unclear, particularly in low-income settings. Reviews of randomised controlled trials (RTCs) performed for the Cochrane Collaboration and the WHO have failed to conclude on the effects of routine iron prophylaxis during pregnancy on pregnancy and birth outcomes.[1 2] There is some evidence that high haemoglobin concentration in late pregnancy may be associated with adverse effects on pregnancy.[3 4] Based on the evidence from non-pregnant populations, it has been suggested that iron may advance the rate of infections.[5–7] The host requires iron for biochemical functioning, but iron may as well promote the replication of infectious agents.[6] For developing country settings which are still plagued by infectious diseases, such as malaria and HIV, the possible association between iron and infections raises serious public health concerns.[8 9]

Previous trials conducted in malarial developing country settings that have evaluated the effects of iron supplementation during pregnancy on maternal and child outcomes have been hampered by small samples, large dropouts and several outcome-related exclusions.[10–14] The findings from the trials were conflicting on the role of prophylactic iron supplementation on birth weight, prematurity, perinatal mortality, incidence of malaria and other pregnancy and birth outcomes. Consequently, the evidence they provide is insufficient in addressing the question of the advantages and disadvantages of prenatal prophylactic iron. The results of studies from non-malarial areas,[15–21] although of better quality, may not be relevant due to different settings.[15–21] Although the results were also conflicting in a number of outcomes, the main findings included slightly longer birth length, longer gestational age and reduced risk of preterm delivery, intrapartum haemorrhage, low birth weight and infant and child mortality in the iron–folic acid group.[22]

This limited evidence and the importance of iron prophylaxis in prenatal programmes call for further investigation on the benefits of prenatal iron supplementation in areas of endemic malaria and with a high prevalence of HIV. Using a pragmatic RCT, we investigated the effects of routine iron prophylaxis throughout pregnancy compared with screening and treatment for anaemia on maternal and child health (MCH) in Maputo, Mozambique. The present paper presents the pregnancy results and interim birth results. About 40% of births were missed by the original data collection method;[22] the missing birth data are currently being retrieved with various complementary methods. The completed birth results will be presented later.

MATERIALS AND METHODS

Study design and population

The details of the PROFEG trial have been described elsewhere[22] and only the main features are given here. The trial was a pragmatic RCT to compare two iron administration policies (routine iron prophylaxis vs screening and treatment for anaemia during pregnancy) on MCH in Maputo, Mozambique. The trial was carried out in two health centres, 1o de Maio in Maputo City, the capital (November 2006—October 2008), and Machava 2 in Maputo Province (June 2007—October 2008), Mozambique. The completion of collection of birth data continued until 2012. The health centre of Machava 2 in Maputo province is close to Maputo city. The population is urban and semiurban, and malaria is endemic in both areas. A seasonal increase of malaria is usually observed towards the end of the rainy season (February–April).[23]

In the study area, all woman were eligible to attend prenatal care. The usual care recommendations at the time of the trial included daily prophylactic iron–folate supplementation (60 mg+400 µg) throughout pregnancy; one dose of mebendazol 500 mg for intestinal parasite; three doses of sulfadoxine pyrimethamine for malaria prophylaxis (started around 20 weeks gestation, or when quickening occurs or when the fetal heart is heard); haemoglobin measurement (Lovibond is routinely used) and syphilis screening at the first prenatal visit and three doses of tetanus vaccine (at the fifth and seventh months and at delivery). If malaria was suspected during prenatal consultations, it was diagnosed by laboratory tests and clinical signs. In most health centres, including our study centres, HIV testing was offered.[22] Antiretroviral (ARV) drugs were provided by various international organisations, but we do not have information of how many women received treatment during pregnancy. The recommendation was to give ARV (Nevirapine) at delivery to prevent mother–child transmission.

Recruitment of study participants

Pregnant women attending their first prenatal visit were the target group. During the routine early morning health education sessions, all women who came for their first prenatal visit were given general information about the study. Recruitment into the study occurred during individual consultations and was carried out by study nurses who were employed and trained by the project. In the 1° de Maio health centre, the women visited the study nurses after their routine prenatal care consultations with the MCH nurses. In Machava, the study nurse and the routine MCH nurse saw the women in the same room. The study nurses checked for the women's eligibility to

participate in the study. The exclusion criteria were: women with high obstetric risk and those aged less than 18 years. If eligible, the nurses asked the women to join the study. Oral and written informed consent was obtained. Three types of women were missed from the study: women whom MCH nurses sent back home because of too early pregnancy, women who did not go to the study nurse and women who refused the study.

Randomisation

The women were randomised into either the Routine iron group (ie, routine iron prophylaxis from the first to the last prenatal visit) or the Selective iron group (ie, regular screening for haemoglobin level and treatment for anaemia). Researcher (OA) used the STATA statistical software (StataCorp LP, Texas, USA) to generate sequential random numbers separately for the two centres, and the women were assigned to either of the groups with a probability of 50%. The codes for the groups were put into sealed and numbered opaque envelopes; the number was the woman's study number and was repeated in the documents in the envelope. The envelope contained a study identification card (yellow for the Routine iron group and pink for the Selective iron group, 10×20 cm) and the informed consent form.

Sample size

We did not have up-to-date reliable baseline data of pregnant women's and newborns' health in Maputo or of the effects of iron on pregnancy and birth outcomes. Thus, we used different estimates of the baseline values for preterm delivery, low birth weight, clinical malaria and perinatal mortality to calculate the sample size, with power (85% and 90%), significance level of 5% and the size of the difference to be detected (20% and 30%). Based on these calculations and the expected feasibility, we decided on a sample size of 2000 women in each group to be enough to measure clinically meaningful effects. The STATA statistical software was used to estimate the sample size. A table showing the various baseline assumptions used for power calculation and in estimating the sample size for the study is included as online supplementary appendix 1.

Interventions

On each prenatal visit, women in the Routine iron group received 30 tablets (supply of 1 month) of 60 mg ferrous sulfate plus 400 µg of folic acid per day combined in one tablet. In the Selective iron group, women's haemoglobin levels were measured at each visit by the study nurses using a rapid haemoglobin measure, HemoCue Hb 201+, (Hemocue AB, Ängelholm, Sweden). If the haemoglobin was 9 g/dl or more, they received 30 tablets of 1 mg of folic acid per day. If their haemoglobin was below the cut-off of <9 g/dl haemoglobin, they received a monthly double dose of iron (60 mg +60 mg) for the treatment of anaemia. Folic acid 1 mg tablets were used because at the time of the trial pure folic acid was not licensed in Mozambique in 400 µg tablets. The tablets were given in a plastic bag having the drug's name and dosage on it.

Data collection and follow-up

Data were collected on standard study data forms by three methods: (1) study nurses abstracted prenatal data from mothers' maternity cards, (2) study nurses asked women additional questions at the time of the prenatal visits and (3) study nurses or researchers collected birth data afterwards from hospital birth records. Delivery nurses were informed of the study and asked to put the delivery cards into a separate study box. The study women were to be identified by the colour of the identification card stapled to their maternity card. However, this did not succeed very well. By excluding estimated late miscarriages (5%), early stillbirths (3%) and home births (10%), we should have received delivery data for 3547 women (82%) of the 4326 women who participated in the trial. We received birth data for only 2258 (64% of the estimated 3547) women.

Outcome measures

The primary outcomes were preterm delivery (delivery <37 weeks of gestation and low birth weight (<2500 g); data on weight came from the birth records; for gestation weeks, various routine data sources were used (see below). Originally, we had malaria activation as a primary outcome, but the pilot showed that it was not feasible. Secondary outcomes were perinatal mortality (as available from our data collection forms; unlikely to cover early stillbirths or neonatal deaths occurring at home); complications during pregnancy and labour; symptoms suggestive of malaria (fever, headache, cold/chills, nausea/vomiting and body aches) and self-reported malaria during pregnancy (the woman was asked for diagnosed malaria since her last visit).

Gestational weeks

In the prenatal visits, routine MCH nurses determined gestational weeks in various ways, even though all ways were not systematically noted down. In the first prenatal visits, the date of the last menstrual period, uterine fundal height, assumed date of delivery and length of gestation (best estimate) were noted. The study nurses abstracted all this information and the best estimate was used in this paper. In birth records, the last menstrual period, date of fertilisation, assumed date of fertilisation and length of gestation were to be given by the delivery nurses. However, these data were very poorly filled and only 681 (30%) of the women with delivery data had their gestational weeks recorded at birth. Thus, the gestational weeks for women without that information were estimated from dates using the following algorithm: gestational weeks at first visit in days+days between the first visit and delivery; the days were then transformed into weeks. For some women (n=196), the date of delivery

was not available. In these cases, the date of discharge from the hospital after delivery (minus the length of stay at the hospital; n=22) or the date of admission to the hospital (n=60 women who did not have the date of discharge) was used.

Adherence

The women were instructed and encouraged at each visit to take the tablets they were given. Women allocated to the Routine iron group could refuse to take the iron tablets; in that case, they were classified as non-compliant with the intervention. Women who belonged in the Selective iron group and who wanted iron (even if their haemoglobin level was not below the cut-off level) were given iron; they were classified as non-compliant with the intervention. The following questions were asked on each visit: 'Was hemoglobin measured?'; 'Was iron/folic acid given to the woman?'; 'Number of iron/folic acid tablets given?'; 'Did the woman take the tablets during the past week?' At each subsequent visit, almost all of the Selective iron women (98%) were measured for haemoglobin using the recommended HemoCue method and the same proportion of women in the Routine iron group were given iron tablets at each subsequent visit.

Statistical analysis

All analyses were performed on an intention-to-treat basis. Twin pregnancies (n=48 pairs) were included in the analysis because their numbers were similar in the two groups and their exclusion did not alter the results. For pregnancy outcomes, all women (n=4326) were included, whereas for birth outcomes, women with birth data (n=2258) were included. Differences in health indicators (fever, headache, cold/chills, nausea/vomiting, body aches, malaria) between the two iron groups at each subsequent visit (up to the fifth visit) during pregnancy were analysed by using binomial generalised estimating equations (GEE) with an exchangeable correlation structure. GEE takes into account the within person correlation in the setting of repeated measures.

Differences in continuously distributed birth outcomes (birth weight, duration of gestation, length of hospital stay) were analysed by using the two sample Student t tests. Categorical outcomes were analysed by using Pearson's χ^2 test or Fisher's exact test (in the case of cells with less than five cases). To estimate the risk ratios of the effect of iron, the binary birth outcomes (low birth weight (<2500 g), preterm birth (<37 weeks), caesarean section delivery, child and maternal ill-health or death at

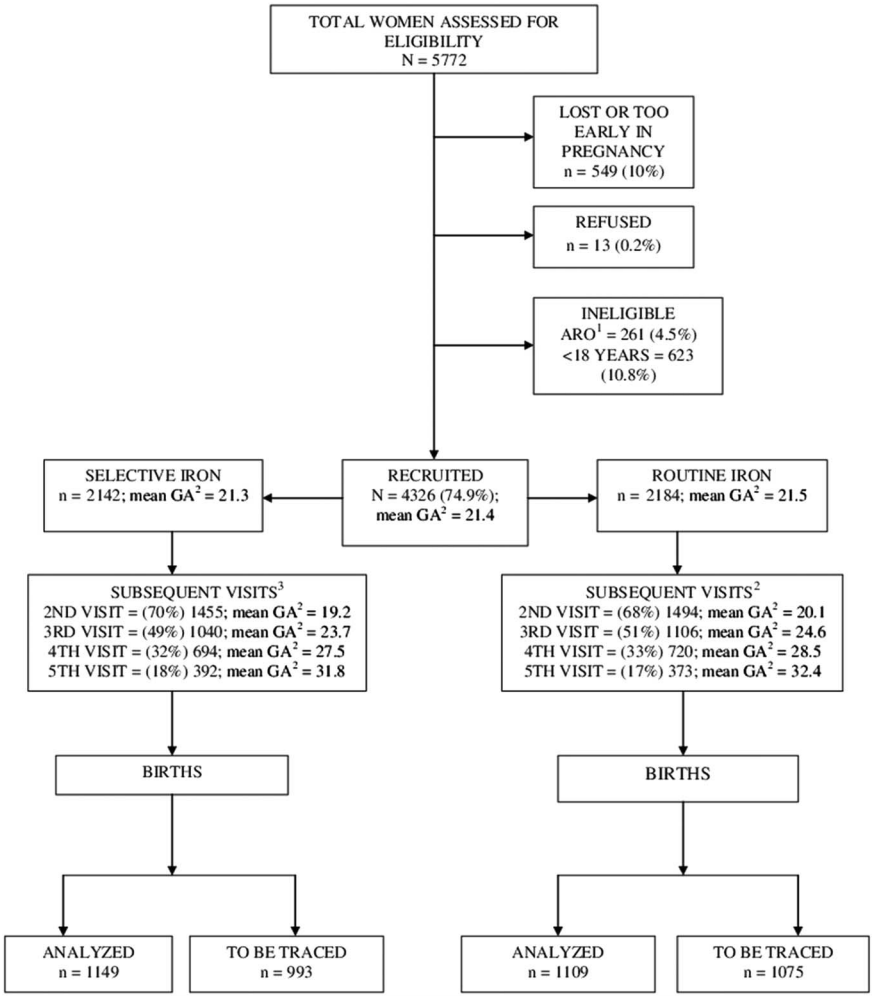

Figure 1 PROFEG Trial flow diagram. [1]ARO, high-risk pregnancy; [2]GA, gestational age in weeks; [3]After recruitment, % were calculated from recruited, n=4326.

Table 1 Characteristics of women at recruitment by availability of delivery data and group allocation, proportions % (numbers)

Characteristics	Delivery data (n=2258)		No delivery data (n=2068)	
	Selective iron (1149) % (n)	Routine iron (1109) % (n)	Selective iron (993) % (n)	Routine iron (1075) % (n)
Maternal age, mean (SD) years	24.6 (5.4)	24.7 (5.3)	25.0 (5.6)	24.6 (5.6)
Maternal age (years) (categorised)				
<20	17.5 (201)	16.5 (183)	15.7 (156)	19.3 (207)
20–24	41.1 (472)	39.9 (443)	39.0 (387)	37.1 (399)
25–29	23.1 (265)	23.3 (258)	23.9 (237)	23.4 (252)
30–34	11.3 (130)	13.8 (153)	12.9 (128)	13.3 (143)
≥35	6.3 (72)	5.6 (62)	7.4 (74)	6.5 (70)
Missing	0.8 (9)	0.9 (10)	1.1 (11)	0.4 (4)
Haemoglobin by HemoCue (g/dl), mean (SD)	9.6 (1.7)		9.6 (1.7)	
Haemoglobin by HemoCue (g/dl), n (%)				
<7.0	6.9 (79)		6.2 (62)	
7.0–8.90	24.6 (283)		25.4 (252)	
9.0–9.90	23.5 (270)		24.4 (242)	
10.0–10.90	21.9 (252)		21.1 (210)	
11.0–11.90	14.1 (162)		13.7 (136)	
≥ 12.0	7.9 (91)		8.4 (83)	
Not measured	1.0 (12)		0.8 (8)	
Previous abortions				
No	87.6 (1007)	86.8 (963)	86.0 (854)	85.4 (918)
Yes	12.1 (139)	12.8 (142)	13.6 (135)	14.5 (156)
Missing	0.3 (3)	0.4 (4)	0.4 (4)	0.1 (1)
Gestational age, mean (SD) weeks	21.6 (5.9)	21.7 (5.6)	21.0 (5.9)	21.3 (5.8)
Gestational age (categorised)				
<16	19.2 (221)	16.4 (182)	21.5 (213)	20.1 (216)
17–20	21.8 (250)	24.2 (268)	22.5 (223)	21.7 (233)
21–26	34.3 (394)	32.6 (361)	31.3 (311)	33.7 (362)
>27	19.7 (226)	19.7 (219)	17.5 (174)	18.2 (196)
No information	58 (5.0)	7.1 (79)	7.3 (72)	6.3 (68)
Previous stillbirths				
No	91.5 (1052)	92.3 (1024)	91.6 (910)	91.0 (978)
Yes	8.2 (94)	7.2 (80)	7.9 (78)	8.9 (96)
Missing	0.3 (3)	0.5 (5)	0.5 (5)	0.1 (1)
Previous deliveries				
None	29.7 (341)	30.3 (336)	29.2 (290)	33.8 (363)
One	31.9 (367)	31.7 (352)	30.6 (304)	28.5 (306)
Two	19.2 (221)	17.8 (197)	17.9 (178)	18.6 (200)
Three or more	18.8 (216)	19.8 (220)	22.0 (218)	19.0 (205)
Missing	0.4 (4)	0.4 (4)	0.3 (3)	0.1 (1)
HIV status				
Negative	81.2 (934)	81.8 (907)	76.7 (762)	79.0 (849)
Positive	18.8 (215)	18.2 (202)	23.3 (231)	21.0 (226)
Twin pregnancy				
No	98.7 (1134)	98.6 (1093)	99.2 (985)	99.2 (1066)
Yes	1.3 (15)	1.4 (16)	0.8 (8)	0.8 (9)
Symptoms during current pregnancy before first prenatal visit				
Fever				
Yes	22.9 (264)	24.4 (271)	28.8 (286)	23.8 (256)
Headache				
Yes	41.5 (477)	43.5 (482)	44.3 (440)	43.0 (462)
Cold/chills				
Yes	18.0 (207)	18.4 (204)	20.6 (205)	18.8 (202)
Vomit/nausea				

Continued

Table 1 Continued

Characteristics	Delivery data (n=2258)		No delivery data (n=2068)	
	Selective iron (1149) % (n)	Routine iron (1109) % (n)	Selective iron (993) % (n)	Routine iron (1075) % (n)
Yes	27.5 (316)	26.9 (298)	29.8 (296)	28.6 (307)
Body aches				
Yes	21.8 (251)	21.3 (237)	23.8 (236)	23.3 (251)
Self-reported malaria				
Yes	5.7 (66)	6.0 (67)	5.9 (59)	6.3 (68)
Had malaria test				
Yes	7.0 (80)	7.1 (79)	8.0 (79)	7.9 (85)

birth, negative fetal heart beat, delivery in a reference health centre, long hospital stay after birth (≥ 2 days) and unavailability of delivery data) were analysed by generalised linear models. The result estimates are presented with 95% CI. Statistical significance was set at $p<0.05$. STATA V.11 statistical software was used for the analyses.

RESULTS

Of the 4326 women recruited to the trial, 2184 were randomly allocated to the Routine iron group and 2142 to the Selective iron group (figure 1). The total number of prenatal visits varied, but the maximum number of visits was seven. The number of follow-up visits was similar in the two groups (figure 1). About 40% of the delivery data were missed when using the original data collection method and the interim birth data were available for 1109 (51%) in the Routine iron group and for 1149 (54% of women) in the Selective iron group.

Table 1 compares maternal background characteristics between groups by the availability of birth data. Mean haemoglobin for the Selective group was similar between those with and without delivery data. The occurrence of symptoms suggestive of malaria (fever, headache, cold/chills, nausea/vomiting and body aches) and self-reported malaria during the current pregnancy prior to the first prenatal visit was similar between the Routine and Selective iron groups. The women in the two groups with and without birth data were comparable.

Between the first and fifth visits, the two groups were similar regarding the occurrence of fever, headache, cold/chills, nausea/vomiting and body aches (table 2). There was a suggestion of increased incidence of self-reported malaria during pregnancy (OR 1.37, 95% CI 0.98 to 1.92) in the Routine iron group (table 2). Table 2 presents the data for the second and third follow-up visits, but this was the case also in subsequent visits (data not shown).

Table 3 presents the distribution of birth data by intervention group and table 4 gives the estimates of the effect sizes on the birth outcomes. The birth outcomes were similar in the two groups. However, there was a suggestion (statistically non-significant) that the Routine iron group had worse outcomes in regard to babies with a negative heartbeat at admission and longer mother's hospital stay after birth (table 3). The effect of iron on the primary outcomes was similar in the two groups.

Table 2 Proportions (%) of women (numbers) with outcomes suggesting malaria during pregnancy, and OR and 95% CIs for group effect, n=4326

Outcomes	Second visit* % (n)		Third visit† % (n)		Between the first and fifth visit‡ OR (95% CI)		
	Selective iron n=1455	Routine iron n=1494	Selective iron n=1040	Routine iron n=1106	Selective iron	Routine iron	p Value
Fever	11.5 (168)	10.0 (150)	11.3 (117)	12.1 (134)	1.00	0.95 (0.81 to 1.11)	0.523
Headache	24.9 (363)	24.3 (363)	24.9 (259)	25.1 (278)	1.00	0.98 (0.87 to 1.10)	0.738
Cold/chills	8.2 (120)	7.0 (104)	6.7 (70)	7.8 (86)	1.00	0.92 (0.76 to 1.11)	0.361
Vomit/nausea	9.1 (133)	10.2 (153)	8.5 (88)	9.6 (109)	1.00	1.09 (0.92 to 1.31)	0.323
Body aches	10.1 (147)	9.2 (138)	10.9 (113)	9.8 (108)	1.00	0.89 (0.75 to 1.06)	0.180
Self-reported malaria	2.4 (35)	3.0 (45)	1.5 (16)	2.2 (24)	1.00	1.37 (0.98 to 1.92)	0.068

*Between the first and second visit.
†Between the second and third visit.
‡The effect estimates calculated by binomial generalised estimating equations (with exchangeable correlation structure) to account for the repeated measures of the outcomes.

Table 3 Birth outcomes by group allocation, percentages, % (numbers) of women or babies or means (SD)

Outcomes	Selective iron (n=1149)	Routine iron (n=1109)	p Value*
Birth weight, mean (SD) grams	2996.3 (508.4)	2989.4 (514.9)	0.752
Birth weight (g), % (n)			0.443
<2500	11.8 (136)	12.8 (142)	
2500–2999	30.6 (351)	31.1 (345)	
3000–3499	40.5 (465)	37.8 (419)	
3500–3999	12.7 (146)	13.8 (153)	
≥4000	3.0 (34)	2.1 (23)	
No information	1.5 (17)	2.4 (27)	
Duration of gestation, mean (SD) weeks	38.3 (4.2)	38.4 (4.0)	0.689
Duration of gestation, % (n)			0.056
<37 weeks	28.8 (331)	27.0 (299)	
≥37 weeks	67.2 (772)	66.9 (742)	
No information	4.0 (46)	6.1 (68)	
Mode of delivery, % (n)			0.235
Normal	87.6 (1007)	89.4 (991)	
Caesarean section	1.3 (15)	2.0 (22)	
No information	11.1 (127)	8.7 (96)	
Child health status at birth, % (n)			0.685
Well	94.0 (1080)	92.1 (1022)	
Ill	0.7 (8)	1.0 (11)	
Dead	1.8 (21)	2.0 (22)	
No information	3.5 (40)	5.0 (55)	
Still birth, % (n)			0.558
No	81.2 (933)	79.7 (884)	
Yes	2.5 (29)	2.9 (32)	
No information	16.3 (187)	17.4 (193)	
Fetal heart beat at admission, % (n)			0.085
Negative	1.6 (18)	2.6 (29)	
Positive	85.6 (984)	85.2 (945)	
No information	12.8 (147)	12.2 (135)	
Mother's health status at birth, % (n)			0.895
Well	95.6 (1098)	94.9 (1052)	
Ill	0.4 (4)	0.4 (4)	
Dead	0.1 (1)	0.2 (2)	
No information	4.0 (46)	4.6 (51)	
Length of hospital stay, mean (SD) days	1.33 (1.21)	1.63 (1.30)	0.075
Length of hospital stay after birth, % (n)			0.103
≤1 day	65.1 (748)	60.7 (673)	
2 days	23.5 (270)	24.2 (268)	
≥3 days	4.0 (46)	5.6 (62)	
No information	7.4 (85)	9.6 (106)	
Place of delivery, % (n)			0.652
1o de Maio (health centre)	44.4 (510)	42.6 (472)	
Machava (health centre)	35.1 (403)	38.2 (424)	
Jose Macamo (hospital)	3.7 (43)	3.6 (40)	
Mavalane (hospital)	14.3 (164)	12.8 (142)	
Central hospital	0.3 (3)	0.3 (3)	
At home	1.1 (13)	1.3 (14)	
On the way to hospital	0.0 (0)	0.2 (2)	
No information	1.1 (13)	1.1 (12)	

*Based on t test for continuous outcomes, Pearson's χ^2 test or Fisher's exact test for categorical outcomes. Subjects with no information were not included in the tests.

The groups were also relatively similar concerning most other outcomes. However, there was a suggestion of more babies with negative fetal heartbeat at admission, longer mother's hospital stay after birth and unavailability of delivery data in the Routine iron group (table 4). By excluding births by caesarean section, the estimates for longer mother's hospital stay remained the same (data not shown).

Table 4 Numbers, proportions (%) and risk ratios (RR, 95% CIs of birth outcomes by iron groups

Outcomes	Selective iron n	Routine iron n	Selective iron (%)	Routine iron (%)	Selective iron	Routine iron RR (95% CI)†	p Value
Primary health outcomes							
Low birth weight (<2500 g)	136	142	11.8	12.8	1.00	1.09 (0.88 to 1.36)	0.431
Preterm delivery (<37 weeks)	331	299	28.8	27.0	1.00	0.96 (0.84 to1.09)	0.185
Secondary health outcomes							
Caesarean section delivery	15	22	1.3	2.0	1.00	1.48 (0.77 to 2.84)	0.238
Negative fetal heart beat at admission	18	29	1.6	2.6	1.00	1.66 (0.93 to 2.96)	0.089
Child ill or dead at birth	29	33	2.5	3.0	1.00	1.20 (0.73 to 1.96)	0.473
Mother ill or dead at birth	5	6	0.4	0.5	1.00	1.25 (0.38 to 4.09)	0.711
Other outcomes							
Delivery in reference centre*	210	185	18.3	16.7	1.00	0.91 (0.76 to 1.09)	0.316
Long hospital stay after delivery (≥ 3 days)	46	62	4.0	5.6	1.00	1.43 (0.97 to 1.26)	0.059
No delivery data	993	1075	46.4	49.2	1.00	1.06 (1.00 to 1.13)	0.060

*Jose Macamo or Mavalane or Central Hospital.
†The estimates were not adjusted for any baseline characteristic because the two groups did not differ from each other at baseline.

DISCUSSION

The results from this trial indicate that routine iron prophylaxis during pregnancy was not advantageous over the policy of screening and treatment for anaemia with regard to pregnancy and birth outcomes. If anything, screening and treatment for anaemia appeared to be better. Among all the trial women, there was a suggestion of an increased risk of self-reported malaria during pregnancy seen in the Routine iron group. The interim birth data suggested a longer hospital stay after birth and higher risk of negative fetal heart beat in the Routine iron group. However, all these differences were statistically non-significant and the complete birth data are needed to conclude any putative effects of iron on birth outcomes.

One of the strengths of our trial is its large sample. So far, this represents the largest trial investigating the benefits of prophylactic iron during pregnancy on MCH in malaria-endemic settings. The compliance of the study nurses with the trial protocol and that of the women with regard to uptake of the iron and folic acid tablets was good, as was the follow-up during pregnancy.[22] However, during pregnancy, we lacked objective measures of malaria; hence, our results may not reflect the putative effect of iron on clinical malaria. The collection of delivery data was challenging, resulting in up to an estimated 40% of missing birth data. We did not realise the extent of the problem until most deliveries had occurred. We are currently tracing the birth data using various methods (abstracting hospital records and death register data and calling women), with results to be reported separately after finalisation.

A comparison of our findings with previous studies conducted in malaria-endemic areas is problematic because of key differences: previous studies have compared iron versus no iron, and our study compares two policies of iron administration: routine prophylaxis versus screening and treatment. Nevertheless, studies from Nigeria[11] and Gambia[12] found no significant effect of iron prophylaxis on malaria; they had used a more reliable measure of malaria (clinical and parasitological analysis). A Ugandan study[14] did not observe any effect of iron supplementation on the incidence of congenital malaria in the offspring. A Bangladeshi study[10] found a difference in preterm delivery (less in the non-iron group), but no association was seen with the other outcomes examined, similar to the Nigerian study,[11] including abortion, hypertension, eclampsia, postnatal complications, birth weight, Apgar scores, prematurity, development of diarrhoea at 6 weeks and perinatal mortality. Other benefits reported with iron prophylaxis include increased mean birth weight,[12 14] reduced incidence of prematurity[12] and increased birth length and Apgar score.[13]

Although more complete birth data are needed to reach firm conclusions, we can speculate that the potential for a higher incidence of unavailable delivery data in the Routine iron group may indicate that these women had more adverse outcomes, such as miscarriage and stillbirths, and consequently did not deliver in the expected health centres. Similarly, the higher likelihood of longer mother's hospital stay after birth in the Routine iron group may also be indicative of more problems at birth. Delivery by caesarean section did not explain the longer hospital stay as the estimate remained the same after excluding the births that occurred by caesarean section.

Anaemia has been associated with MCH risks,[24–26] and the association between iron and increased risk of infections[5–7]calls for more definitive evidence on the benefits of iron prophylaxis during pregnancy in settings with increased infectious diseases where infections remain a major cause of maternal and child mortality.[8 9] Our trial in Maputo, Mozambique is an attempt to investigate whether routine iron prophylaxis during pregnancy

is more effective than screening and treatment for anaemia in improving MCH in an area of endemic malaria and HIV.

CONCLUSIONS

These interim results from this pragmatic RCT indicate that routine iron prophylaxis during pregnancy did not suggest better MCH outcomes than the policy of screening and treatment for anaemia. If anything, screening and treatment for anaemia appeared to be better. Complete birth data are needed for a firm conclusion. Which of the two methods, Routine or Selective iron prophylaxis, is more feasible will be discussed in later publications.

Author affiliations
[1]Health Services and Policy Research, National Institute for Health and Welfare, Helsinki, Finland
[2]Department of Community Health, Eduardo Mondlane University, Maputo, Mozambique
[3]School of Health Sciences, University of Tampere, Tampere, Finland
[4]Department of Physiological Sciences, Eduardo Mondlane University, Maputo, Mozambique
[5]Ministry of Health, Maputo, Mozambique

Contributors BIN, EH, ER and SP designed, analysed and wrote the paper. EH designed and was responsible for the conception of the PROFEG Trial. BC, CS, EH, FA, GS, JC, MD, MN, OA and SP participated in the planning of the PROFEG Trial and made substantial contribution to its execution and participated in interpreting the results and critically reviewing the manuscript. ER and OA were responsible for data preparation and cleaning.

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